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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KIM, JENNIFER M	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 10/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/621,229	IBANEZ, JUAN JOSE LEGARDA	
	Examiner	Art Unit	
	Jennifer Kim	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 August 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-30 and 46-58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-30 and 46-58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed August 23, 2006 have been received and entered into the application.

Action Summary

The rejection of claims 17-45 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 1,3-6 and 8-13 and 28 of copending Application No. 11/111,435 is being maintained for the reasons stated in the previous Office Action and the rejection is modified in this Office Action to include newly added claims and to exclude cancelled claims.

The rejection of claims 30 and 44 rejected under 35 U.S.C. 112, first paragraph, is hereby expressly withdrawn in view of Applicant's amendment.

The rejection of claims 17-26, 29, 31-40, 43 and 45 under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record is being maintained for the reasons stated in the previous Office Action and the rejection is modified in this Office Action to include newly added claims and to exclude cancelled claims.

The rejection of claims 27-28, 41 and 42 under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record as applied to claims 17-26, 29, 31-40, 43 and 45 above, and further in view of Opitz (U.S.Patent No. 5,519,017) is maintained for the reasons stated in the previous Office Action and the rejection is modified in this Office Action to include newly added claims and to exclude cancelled claims.

The rejection of claims 30 and 44 under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record as applied to claims 17-26, 29, 31-40, 43 and 45 above, and further in view of Aguirre et al. (Alcohol, 1990) is being maintained for the reasons stated in the previous Office Action and the rejection is modified in this Office Action to include newly added claims and to exclude cancelled claims.

Applicant's amendment necessitated additional rejection presented in this Office action.

Response to Arguments

Applicant's arguments filed August 23, 2006 have been fully considered but they are not persuasive. Applicant argues that it is important to note that alcohol withdrawal syndrome and alcohol dependency are two different conditions and Gerra and Nutt teach methods of treating alcohol withdrawal symptoms and not alcohol dependency. This is not persuasive because Gerra clearly teaches treatment of the **ethanol addicts** (16 men and four women: age range 34 to 56 years) **with dependency** administering

flumazenil. Gerra teaches these ethanol addicts with dependency experiencing symptoms of ethanol withdrawal were treated with same active agent, flumazenil. Therefore, this teaching encompasses Applicant's claimed treatment of alcohol dependency because the ethanol addicts treated by Gerra are dependent on ethanol for at least three years. (see table under Dependency, Evaluating using DSMIV2 criteria: symptoms, in Applicant's response page 8). Applicants argues that there is clear distinction between withdrawal symptoms and drug craving, and alcohol withdrawal syndrome and alcohol dependency is shown by the different evaluation criteria for dependency and withdrawal. This is not persuasive because the distinction between withdrawal symptoms and alcohol dependency and different evaluation method do not alter the fact that the same compound (flumazenil) has been previously used by Gerra et al. to treat **alcohol addicts with dependency** having withdrawal symptoms. The patient (alcohol addicts), condition (dependency with withdrawal symptoms) to be treated are the same. An explanation of why that symptoms/conditions differ in the same patient (ethanol addicts with **dependency**) does not make unobvious the same treatment of the same conditions encompassed by the claims. Applicant argues that there is no motivation from the cited prior art to experiment with different administration dosage and timing intervals between 1 and 24 hours because the toxicology of flumazenil is already known. This is not persuasive because the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge

generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, The references teach the extension of time intervals of flumazenil from 1 minutes to 6 hours and to optimize known intervals and known effective amounts of given compound is well with the skilled in the art as there is many reasons for varying dosages and dosing intervals such as concurrent medical requirements and therapy that increase the absorption of the compound resulting in toxicity as an example only. The toxicology of flumazenil is well known in the art, but it is up to and within routine practice of one of ordinary skill in the art to optimize the dosing intervals and effective amounts and consider all requisites medical condition of the patient to be treated in order to successfully deliver the compound in safe manner so that the patient does not develop toxicity of flumazenil. Applicant argues that Opitz fails to make up for the deficiencies of Gerra Nutt; and there is no indication from Aguirre that decreases in b-endorphin levels are necessarily caused by alcoholism. This is not persuasive because Opitz reports that clomethiazole, piracetam and disulfiram are the drugs used to control the influence of alcohol and the alcoholism. This teaching is a motivation to combine clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency in order to achieve at least an addictive effect in the treatment of alcohol dependency. The motivation of combining the components flows from their individually known common utility. (see In re Kerkhoven). Further, Aguirre et al. teach that decrease level of beta-endorphin caused chronic consumption of alcohol in alcoholism. Therefore, it would have been obvious to one of ordinary skill in the art at

the employment of flumazenil for the treatment of alcohol dependency as modified by Nutt et al. would result in the reduction in alcohol consumption because flumazenil is known to raise the concentration of beta-endorphin level. Thus, the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17-26, 29, 46-55 and 58 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over 1,3-6 and 8-13 and 28 of copending Application No. 11/111,435. The instant application and

copending application are directed to same subject matter comprising treatment of alcohol dependency such as alcohol abuse with same effective daily dose with administration of same active agent (flumazenil). Instant claims differ by amounts sequentially administered and the time intervals. However, the amounts of daily dosages divided to sequentially administer to the patient and the time intervals are obvious modification since they are within the knowledge of one of ordinary skill in the art. One of ordinary skill in the art would optimize the dosing intervals and to divided known daily dosage of treating alcohol dependency according to patient's condition, severity and the factors concerning concurrent medical ragmen.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 17-26 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record.

Gerra et al. teach ethanol addicts with dependency were treated with flumazenil in dose of **2mg/day divided into four doses** (0.5mg per dose) **IV (intravenous, parenteral) every 6 hours** (sequential) for 48 hours. (Abstract, page 63 lines 32-33). Gerra et al. teach that significant improvement in **alcohol withdrawal symptoms including tremors, sweating, nausea, depression anxiety and restlessness** shown by data when the patients were treated with flumazenil. (page 65 lines 7-10). Gerra et al. teach that some patients experienced **somnolence** during first day of the treatment with flumazenil. (page 65, first full paragraph).

Gerra et al. do not teach the specified time intervals and the specified portion of amounts set forth in claims 17, 19, 20 and 24 administering flumazenil under sedation set forth in claims 29 and 43 and administering additional agent set forth in claim 26.

Nutt et al. teach that **2mg dose** of flumazenil was administered as an **IV infusion** over **1 minute** to alcoholics in acute withdrawal. (abstract, page 338, 3rd and 4th full paragraphs). Nutt et al. teach that the other drug (additional agent) was administered after flumazenil. (page 338, 4th paragraph).

It would have been obvious to one of ordinary skill in the art to optimize the time intervals and dividing portions of known daily effective dose of flumazenil 2mg/day taught by Gerra et al. because flumazenil is effective for the treatment of symptoms of alcohol dependency in divided doses and administered in time intervals of 6 hours by Gerra et al. and Nutt et al. teach that flumazenil can also be administered over 1 minute. These references teach the extension of time intervals of flumazenil can be 1 minute to 6 hours. Accordingly, one would have been motivated to optimize the well-known

effective daily dose of flumazenil for the treatment of alcohol dependency within any time intervals between 1minutes taught by Nutt et al. to 6 hour time period taught by Gerra et al. in any divided total daily dose for the treatment of alcohol dependency because as anyone of ordinary skill in the art will appreciate, preferred divided dosages and intervals are merely exemplary and serve as useful guideposts for the physician. There are, however, many reasons for varying dosages, and dosing intervals including by orders of magnitude; for instance, a patient having multiple dosing regimen or one having noncompliant would require a correspondingly dosing intervals. Furthermore, it is routine during animal and clinical studies to dramatically vary dosage to obtain data on parameters such as toxicity. One would have been motivated to optimize the dosing intervals and optimize the daily amounts in portions to achieve an ultimate therapeutic regimen needed for individual patient's medical requirements.

With regard to administration of flumazenil under sedation set forth in claims 29 and 43, it would have been obvious to one of ordinary skill in the art to administer flumazenil, particularly while the patient is in sleep (sedation) because flumazenil causes somnolence as taught by Gerra et al. One would have been motivated to employ flumazenil while the patient is in sleep in order to take an advantage of side effect of flumazenil causing somnolence reported by Gerra et al. to achieve an additive benefit of somnolence while patient is in sleep. One would have been motivated to employ flumazenil while the patient is in sleep in order to conveniently take advantage of somnolence effect of flumazenil.

With regard to administration of additional agent after the administering flumazenil for the treatment of alcohol dependency is obvious because Nutt et al. teach that other agent (additional agent) is routinely administered after flumazenil in treatment of Nutt et al. One would have been motivated to employ additional agent for the treatment of alcohol dependency taught by Gerra et al. as modified by Nutt et al. in order to achieve routine effect of ameliorating alcohol dependency as taught by Nutt et al.

Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record as applied to claims 17-26 and 29 above, and further in view of Opitz (U.S.Patent No. 5,519,017).

The teachings of Gerra et al. and Nutt et al. as applied as before.

Gerra et al. and Nutt et al. do not teach the specified additional agent such as clomethiazole set forth in claims 27, 41 and piracetam and disulfiram set forth in claims 28 and 42.

Optiz reports that clomethiazole, piracetam and disulfiram are the drugs used to control the influence of alcohol and the alcoholism and that clomethiazole is used for the alcoholic delirium, piracetam is used for the palliatives or the acute alcohol withdrawal and disulfiram is the most frequently used for the treatment of alcoholism. (column 1, lines 37-55).

It would have been obvious to one of ordinary skill in the art to employ other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency taught by Gerra et al. as modified by Nutt et al. One would have been motivated to incorporate other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency in order to achieve at least an additive effect in treatment to alcohol dependency and achieve the expected benefit of the palliative or anti delirium effect of the each of the agent in alcohol withdrawn treatment. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)) in treatment of alcoholism.

Claim 30, 46-55 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record as applied to claims 17-26 and 29 above, and further in view of Aguirre et al. (Alcohol, 1990).

The teachings of Gerra et al. and Nutt et al. as applied as before and additional teaching of Gerra et al. as follows.

Gerra et al. teach that there is observation of significant rise in plasma concentrations of beta-endorphin after administration of flumazenil. (page 65, lines32-25).

Gerra et al. and Nutt et al. do not teach the reduction or elimination of the desire to drink alcohol by flumazenil.

Aguirre et al. teach that the decrease level of beta-endorphin is a cause chronic consumption of alcohol in alcoholism. (abstract).

It would have been obvious to one of ordinary skill in the art that the employment of flumazenil for the treatment of alcohol dependency as modified by Nutt et al. would result in the reduction in alcohol consumption because Gerra et al. teach that flumazenil significantly raise the plasma concentration of beta-endorphin and Aguirre et al. teach that decreased level of beta-endorphin caused alcohol consumption. One would have been motivated to employ flumazenil as taught by Gerra et al. as modified by Nutt et al. for the treatment of alcohol dependency to reduce the alcohol consumption in order to achieve an expected benefit of flumazenil's effectiveness in eliminating the cause of alcohol consumption by increasing beta-endorphin level in alcoholics.

Claim 56 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gerra et al. (Current Therapeutic Research, 1991) of record in view of Nutt et al. (Alcohol & Alcoholism, 1993) of record and further in view of Aguirre et al. (Alcohol, 1990) as applied to claims 30, 46-55 and 58 above, and further in view of Opitz (U.S.Patent No. 5,519,017).

The teachings of Gerra et al., Nutt et al., and Aguirre et al. as applied as before.

Above references do not teach the specified additional agent set forth in claims 56 and 57.

Optiz reports that clomethiazole, piracetam and disulfiram are the drugs used to control the influence of alcohol and the alcoholism and that clomethiazole is used for the alcoholic delirium, piracetam is used for the palliatives or the acute alcohol withdrawal

and disulfiram is the most frequently used for the treatment of alcoholism. (column 1, lines 37-55).

It would have been obvious to one of ordinary skill in the art to employ other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency taught by Gerra et al. as modified by Nutt et al. and Aguirre et al. One would have been motivated to incorporate other additional agent such as clomethiazole, piracetam or disulfiram for the treatment of alcohol dependency in order to achieve at least an additive effect in treatment to alcohol dependency and achieve the expected benefit of the palliative or anti delirium effect of the each of the agent in alcohol withdrawn treatment. The motivation for combining the components flows from their individually known common utility (see In re Kerkhoven, 205 USPQ 1069(CCPPA 1980)) in treatment of alcoholism.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited references. The claims are therefore properly rejected under 35 U.S.C. 103.

None of the claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Kim whose telephone number is 571-272-0628. The examiner can normally be reached on Monday through Friday 6:30 am to 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sreenivasan Padmanabhan
Supervisory Primary Examiner
Art Unit 1617

Jmk
September 12, 2006